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CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			SAJJADI, FEREYDOUN GHOTB	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/765,520	BENJAMIN, THOMAS L.
	Examiner Fereydoun G. Sajjadi	Art Unit 1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 27 January 2004.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-19 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-19 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 1/27/2004 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

This action is in response to the preliminary amendment filed January 27, 2004, canceling claims 20-28. Claims 1-19 are pending in the application and under current examination.

Claim Objections

Claims 19 is objected to, because the claim contains an error in the spelling of the term “human”, and the claim does not end with a period. See MPEP 608.01(m) [R-3].

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 a) recites, “infecting a normal cell and abnormally proliferating cell a collection of uncharacterized mutant viruses”. It is not clear how a collection of viruses is determined to be mutant when they are uncharacterized. It is well known in the art that viruses undergo mutations. Therefore a wild type population of uncharacterized viruses may by extension qualify for said collection. It is further not clear how any collection of mutant viruses of any type may infect said cells, as cells may not be permissive for said infection and further, no active steps are recited. MPEP 2173.05(q) states: Attempts to claim a process without setting forth any steps involved in the process generally raises an issue of indefiniteness under 35 U.S.C. 112, second paragraph. *Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986).*

Claim 1 d) recites “screening to identify the cellular protein which interacts”. It is not clear how said screening is achieved. No active steps or descriptions for said screening or identification are provided in the claim.

Claim 1 d) additionally recites the limitation “the wild type viral protein”. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 is unclear. Claim 2 recites, “wherein the abnormally proliferating cell is uncharacterized.” It is not clear as to what specific limitation or characteristic said characterization is referring. Therefore the metes and bounds of characterization remain undefined.

Claims 2-11 depend from claim 1.

Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on any virus that may be mutated or any virus that may be defined as T-HR (tumor host range). As such, the claims encompass numerous viruses, both known and yet to be discovered. The specification defines tumor host range mutant virus (T-HR mutant), as a virus that has a reduced ability to replicate and disseminate in normal cell, relative to replication of a wild-type virus in the same type of cell, but is able to replicate and disseminate in a cell having abnormal proliferation (p. 4). The specification discloses a single virus mutant from the polyoma strain that is mutagenized and shown to grow poorly on primary BMK cells, but grew well on transformed cells (Example 1, pp. 25-27). Moreover, the methods of the present invention rely on the critical ability to discern differential growth properties of a mutant versus a wild type virus from a collection of mutant viruses. The determination of differential propagation in different cell types is therefore limited to plaque forming or oncolytic viruses. However, the foregoing is not a shared property of all viruses.

The specification provides no additional viral strains that are randomly mutated to demonstrate that such viruses were included in the present invention. Moreover, Applicant’s

specification provides no examples of additional mutants of polyoma that may be defined as T-HR. The claims encompass a large number of viral strains, and thus constitute a claimed genus that encompasses other viruses, yet to be discovered, and since the specification only discloses a single mutant polyoma virus species, the disclosed structural features of said virus do not constitute a substantial portion of the claimed genus. As such, the Artisan of skill could not predict that Applicant possessed any additional species, except for the polyoma virus. Hence, only the mutant polyoma virus could be demonstrated as possessed.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlfors*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims as reading on viruses yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the genus of numerous viral strains. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of numerous virus strains, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 1-11 and 13-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying an mSal2 protein involved in the susceptibility to proliferative disease, said method comprising transfecting a normal cell and an abnormally proliferating cell *in vitro*, with a collection of plasmids carrying mutant polyoma viruses; does not reasonably provide an enablement for a method of, identifying a cellular protein involved in the susceptibility to proliferative disease *in vitro* or *in vivo*, said method comprising infecting a normal cell and an abnormally proliferating cell with a collection of uncharacterized mutant viruses of any type; identifying a mutant virus from the collection that can grow in said abnormally proliferating cell and can not grow in said normal cell; and identifying the mutated viral gene or mutated protein in said virus. The specification is further not enabling for a method of determining the presence or absence of any of numerous possible alterations in the genetic material of a cell that may include silent mutations, comprising

determining whether a cell can act as a permissive host for the propagation of “characterized” T-HR mutant, wherein said mutant can propagate in an abnormally proliferating cell and not in a normal cell, and wherein said mutant is unable to propagate in a cell carrying a mutation in the retinoblastoma or p53 gene, as broadly claimed.

In determining whether Applicant’s claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform “undue experimentation” to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states at page 1404:

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

MPEP § 2164.04 states: “[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection.”

The Nature Of The Invention And Breadth Of Claims

Claims 1-11 encompass a method of, identifying a cellular protein involved in the susceptibility to proliferative disease, said method comprising infecting a normal cell and an abnormally proliferating cell with a collection of uncharacterized mutant viruses; identifying a mutant virus from the collection that can grow in said abnormally proliferating cell and can not grow in said normal cell; and identifying the mutated viral gene or mutated protein in said virus, which allows said virus to grow on said abnormally proliferating cell; and screening to identify the cellular protein which interacts with the wild-type viral protein, but not said mutated viral protein. Claims 13-19 embrace a method of determining the presence or absence of an alteration in the genetic material of a cell, comprising determining whether a cell can act as a permissive

host for the propagation of characterized T-HR mutant, wherein said mutant can propagate in an abnormally proliferating cell and not in a normal cell, and wherein said mutant is unable to propagate in a cell carrying a mutation in the retinoblastoma or p53 gene. However, methods for identifying genetic mutations in a cellular protein involved in susceptibility to proliferative disease using any type of viruses *in vitro* or *in vivo*, or methods identifying any cellular mutation, require an enabling disclosure.

The Amount Of Direction Or Guidance Presented And Working Examples

The instant specification discloses a “collection of uncharacterized mutant viruses” as referring to a sample of viruses where at least one of the viruses in a collection of at least 1000 viruses (e.g. 0.1%) carries at least one mutation in at least one of the genes of the viral genome. (lines 1-3, p. 5). Example 1 describes randomly mutagenized virus prepared by passage of a plasmid containing wild-type polyoma viral DNA through error prone Mut D strain of *E. coli*, followed by excision of the viral genome and transfection into TCMK-1 cells, to obtain a frequency one mutant in several thousand plaques tested (lines 16-24, p. 29). However, the method of instant claim 1 a) recites infecting cells with mutant viruses. Therefore, the claim is contrary to the teachings of the instant specification, as infection requires the presence of viral particles, whereas transfection by isolated naked DNA is a separate and distinct process.

The specification is silent on the utilization of any other viruses or other cells or cell lines in the identification of a mutant host range virus. The specification only describes the selection of a single polyoma T-HR virus (TMD25) in a few mouse cell lines *in vitro*. (TMD25 was characterized as C-terminal mutant of the viral large T antigen.) Moreover, the specification teaches: “TMD25 mutants grew poorly, if at all, on primary BMK cells” (line 3, p. 27). Therefore the identification of a mutant virus from a collection that can grow in an abnormally proliferating cell and can not grow in a normal cell (as claimed) is not supported by the specification, as a T-HR virus may still grow, albeit poorly on “a normal” cell.

The specification states that “The use of mutant adenoviruses unable to inactivate p53 or the retinoblastoma (pRb) to kill cancer cells lacking one of these proteins has been previously described...It was well known prior to these observations that these two genes are mutated in a variety of cancers.” (lines 5-8, p. 2). The specification is further silent on the presence or absence

of p53 and Rb proteins in the cell lines permissive for TMD25 growth. Therefore, the inability of a T-HR mutant to propagate in a cell carrying a mutation in the retinoblastoma or p53 genes (as claimed) is unsubstantiated. Further, the prior art of Freund et al. had demonstrated the interaction of pRB with the polyoma large T antigen (*supra*). Example 2 (p. 27) identifies the TMD-25 mutation responsible for its “tumor host range” as localized to the carboxyl-terminal half of polyoma large T antigen. Hence, the wild type viral protein that corresponds to the mutant viral protein, must necessarily be the wild type large T antigen that interacts with pRB (contrary to claim 3).

The specification further fails to disclose adequate representations of a correlation between the ability of a cellular protein to complement deficient viral replication of any type of virus, and its function as a proto-oncogene. The specification identifies a single protein (mSal2, Example 8), with the ability to suppress growth of the SKOV3 cell line. The ability to complement defective replication of any virus type does not necessarily require the complementing cellular protein to be involved in the susceptibility to proliferative disease, as instantly claimed. Therefore, it would require further experimentation to demonstrate that numerous possible complementing cellular proteins in fact possess such ability, as instantly claimed. It would require yet further experimentation to find and characterize “normal” and “abnormal”, matched cells of any lineage to enable the differential screening envisioned. The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the person of skill in the art (Artisan) would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to create, characterize the sizable number of T-HR mutant viruses that may be obtained from numerous strains of viruses envisioned in the instant application based on their growth characteristics in a multitude of different cell types, *in vitro* or *in vivo*, and to further identify cellular proteins that contain mutations complementing the growth abilities of said T-HR mutants, wherein the cellular mutations are not in the retinoblastoma or p53 genes, yet involved in the susceptibility to proliferative disease, or a method of determining the presence or absence of any of numerous possible genetic alterations possible in a cell (as a multitude of genes and their products are redundant in a transformed cell), for the methods of the instant application.

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses one polyoma virus having a mutation in the large T antigen and its complementation by the cellular protein mSal2.

The State, The Level Of Skill, & The Unpredictability Of The Art

The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art is effectively summarized by the references of Freund et al. (J. Virol. 68:7227-7234; 1994), Kirkegaard et al. (J. Virol. 64:185-194; 1990); Androphy et al. (U.S. Patent No: 6,296,853), Zauderer et al. (U.S. Pat. Pub. No: 2003/0022157), and D’Andrilli et al. (Clin. Cancer Res. 10:8132-8141; 2004)

Freund et al. describe the growth properties of polyomavirus large T-antigen mutants that are unable to bind the RB protein and grow poorly on primary mouse BMK cells, but grow on NIH 3T3 cells. (Abstract). Freund et al. state: “Interaction of polyomavirus large T antigen with the retinoblastoma tumor suppressor protein pRB is essential for activation of the cell cycle and for production of progeny virus following infection of normal resting mouse cells. The interaction is sufficient, even in the absence of functional middle and small T, for induction of cellular DNA synthesis during polyomavirus lytic infection of primary BMK cells” (second column, p. 7232).

Kirkegaard et al. describe the generation of conditional poliovirus mutants by random mutagenesis followed by selection on the basis of their host range phenotype, showing the production of large plaques on HeLa cells compared to wild type virus (Abstract). Androphy et al. teach the discovery of protein-protein interactions between the papillomavirus (HPV) protein E6 and certain cellular proteins such as p53 that lead to an oncogenic outcome (columns 1 and 2). Additionally described is the methodology utilizing the yeast two hybrid system to identify the cellular proteins that interact with the E6 protein (Example 1, column 52). Zauderer et al. describe methods for producing a library of polynucleotides introduced in linear DNA viruses and the selection of polynucleotides of interest based on cell nonviability (Abstract). Zauderer et

al. specifically describe the application of their methods for the isolation of oncogenes and tumor suppressor genes (first column, p. 1), and wherein the modified virus genome is defective in an essential gene and the host cell comprises a complementing copy of said essential gene (claim 96). D'Andrilli et al. in reviewing the state of the prior art regarding cell cycle regulatory genes involved in ovarian cancer, describing a number of different regulatory genes and their downstream products involved in disease pathways, including various cyclins, the retinoblastoma (Rb) gene, as well as p53, concluding that further studies are required to understand and further utilize the existing knowledge in developing therapeutic strategies (entire disclosure). Additionally, given the numerous redundant cellular mutations that occur in the proliferative cycle of a transformed cell, the discovery of a cellular gene by mutation analysis is difficult and unpredictable and entails undue experimentation.

The prior art does not describe the ability to generate and screen for any and all types of conditionally replicating mutant viruses that cannot grow on normal cells, but proliferate on abnormally proliferating cells. To effectively screen for these differential characteristics, a virus must have not only the ability to grow in abnormal cells, but also to lyse the abnormal cells, thereby forming discernable plaques. The lytic action of the mutant virus can then be differentiated on a lawn of abnormal cells when compared to infection of a lawn of normal cells. However, not all viruses have this plaque forming ability, and it would require undue experimentation to discover and characterize numerous mutant virus strains, displaying such characteristics.

Because of the immaturity of the art, its complexity, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The claims of the instant application are drawn to methods of identifying cellular proteins using numerous strains of viruses and various cellular genetic alterations, not apparent from the disclosure of the invention. Therefore, in light of the guidance provided by the disclosure of the application and the unpredictability of the art, it would require undue experimentation by the skilled Artisan to carry out the experiments required to demonstrate that numerous types of uncharacterized viruses may be utilized that have the ability to infect and grow on an abnormally proliferating cell of any lineage, and not in a normal cell, and having further identified a

complementing cellular protein that interacts with the “wild-type protein”, to additionally demonstrate that said complementing protein is a cellular protein involved in the susceptibility to proliferative disease. It would require additional undue experimentation to determine the presence or absence of any alteration in the genetic material of any cell based on the propagation of a mutant T-HR virus that is not able to propagate in a cell carrying a mutation in the Rb or p53 genes. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Quantity Of Experimentation

The quantity of experimentation in the area of transforming viruses and oncogenes is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is enabled for the method of identifying the numerous cellular proteins that may be involved in the susceptibility to proliferative disease using numerous viral strains. It would require undue experimentation to identify adequately matched, paired cell types so that differential morphogenetic properties of “normal” and “abnormal” may be properly assigned. It would require further require undue experimentation to screen for a genus of viruses of any type or strain that need to be subjected to mutation and further screened for their differential growth properties, so as to be defined as tumor host range. These experiments likely entail unpredictable outcomes. It would also require additional experimentation to determine the presence or absence of any type of genetic alteration of a cell, involving any genes, including alterations that may not be involved in the growth of a mutant T-HR virus. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Analysis And Summary

Applicant is therefore enabled for a method of identifying an mSal2 protein involved in the susceptibility to proliferative disease, said method comprising transfecting a normal cell and an abnormally proliferating cell *in vitro*, with a collection of plasmids carrying mutant polyoma

viruses. In the instant case, and for the specific reasons cited above, in a highly unpredictable art where screening of a library of mutated viruses is limited to conditionally replicating plaque forming viruses, and where the correlation between the ability of any mutant virus to replicate and a complementing cellular protein serving as a proto-oncogene remains tenuous, and where the inability of a wild-type protein corresponding to a mutant T-HR protein, to interact with pRB remains to be demonstrated, together with the large quantity of research required to define these unpredictable variables, including the determination of the presence or absence of any type of genetic alterations in a cell, and the lack of guidance provided in the specification regarding the inability of a mutant T-HR to grow in a normal cell, it is the position of the examiner that it would require undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7, and 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Freund et al. (J. Virol. 68:7227-7234; 1994).

Claim 1 is drawn to a method of identifying a cellular protein involved in the susceptibility to proliferative disease, said method comprising the steps of:

- a) infecting a normal cell and an abnormally proliferating cell with a collection of uncharacterized mutant viruses;
- b) identifying a mutant virus from the collection that can grow in said abnormally proliferating cell and can not grow in said normal cell; and

- c) identifying the mutated viral gene or mutated protein in said virus, which allows said virus to grow on said abnormally proliferating cell; and
- d) screening to identify the cellular protein which interacts with the wild-type viral protein, but not said mutated viral protein.

The specification defines a collection of uncharacterized mutant viruses as a sample of viruses where at least one of the viruses in a collection of at least 1000 viruses (e.g. 0.1%) carries at least one mutation in at least one of the genes of the viral genome (lines 1-3, p. 5).

Freund et al. teach the derivation of polyomavirus mutants by mutagenesis (second column, p. 7227). The infection of NIH 3T3 cells (abnormally proliferating) and mouse BMK cells (normal) with mutant viruses at different multiplicities of infection are described in the first column of p. 7228. (Therefore the limitations of instant claim 1a) are specifically taught). As polyomavirus mutants are demonstrated to differentially infect normal and abnormally proliferating mouse cells, they have a mammalian host range (the limitation of claims 7 and 9).

The authors state that these mutants grow poorly on primary mouse cells yet grow well on NIH 3T3 cell line (Abstract) and that the mutants can be identified by mutations in the virus large T antigen (second column, p. 7228; Fig. 1). Thus teaching the limitation of instant claim 1b) and 1c). The authors additionally state that the mutations of large T in the mutant viruses prevent binding to the cellular Rb protein both in vivo and in vitro binding assays (second column, p. 7229 and first column, p. 7230, bridging). Several experiments are described to show that the cellular Rb protein interacts with the wild type large T antigen, but not the mutated viral T antigen. These included complementation of BMK cells with SV40 large T antigen (first column, p. 7230, overexpression of Rb gene in different cell lines, demonstrating that wild type Rb alone is sufficient to restrict the growth of the polyomavirus mutants (first column, p. 7230), and immunoprecipitation of wild-type polyomavirus large T in NIH 3T3 and BMK cells, showing complexation with the wild type T antigen and pRb in BMK cells, but not in NIH 3T3 cells (first column, p. 7231). As these experiments constitute various screens for interactions of a cellular protein with wild type and mutant virus, they teach the limitations of claim 1d).

The authors state: “ pRB-binding polyomavirus mutants have a host range determined by expression of the targeted tumor suppressor gene in the host” (first column, p. 7233), hence the mutant viruses are tumor host range viruses (the limitation of claim 12). The pRB protein is

characterized as both a proto-oncogene (as mutations in the Rb gene can confer an oncogenic state) and a tumor suppressor protein and thus satisfies the limitations of claims 10 and 11.

Therefore, Freund et al. teach each and every limitation of claims 1, 7, and 9-12, absent evidence to the contrary.

Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Pyles (WO 98/42195; publication date: 1.10.98).

Claim 12 is a product by process claim that is directed to a tumor host range (or mutant) virus. A tumor host range virus is defined in the instant specification as “a virus that has a reduced ability to replicate and disseminate in a normal cell, relative to the replication of a wild-type virus in the same cell type of cell, but is able to replicate and disseminate in a cell having abnormal proliferation.” (p. 4, under definitions).

Pyles teaches “mutant, replication competent HSV-1 viruses that can enter a tumor cell *in situ*, make multiple copies, lyse the tumor cell and spread to additional tumor cells with relatively minor effects on the surrounding normal cells.” (lines 2-4, p. 11). Pyles further teaches that the differential replication ability of the mutant herpes simplex virus, versus the wild type is due to two mutations in the viral genome that distinguish its selectivity for brain tumor cells versus surrounding normal brain cells (lines 16-22, p. 11). Hence, each and every limitation of the mutant virus of claim 12 is anticipated by Pyles, absent evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 3-6, and 13-14 are rejected under 35 U.S.C. §103(a) as being unpatentable over Freund et al. (J. Virol. 68:7227-7234; 1994, in view of Androphy et al. (U.S. Patent No: 6,296,853; filed Aug. 26, 1999).

Freund et al. describe the identification of several cellular proteins that interact with polyomavirus protein, as outlined *supra*. Freund et al. do not teach that one of the cellular protein that interacts with the viral protein is not a retinoblastoma tumor suppressor protein, but state: “The finding that pRB-binding polyomavirus mutants have a host range determined by expression of the targeted tumor suppressor gene in the host raises the possibility that a systematic study of the virus host range might help uncover other host genes that act negatively in regulating cell cycle progression and that are potentially new tumor suppressor genes... Virus mutants defective in inducing cell cycle activation or progression would be able to grow well only in those cells that have lost the growth-restraining function(s). Tumor cells, particularly those of spontaneous or unknown origin, would be good candidates for permissive hosts in such a search.” (first paragraph, p. 7233). Thus, providing the motivation to extend their studies to the generation and screening of additional mutants.

Androphy et al. teach the discovery of several cellular proteins different from Rb and p53, that are involved in protein-protein interactions with the papillomavirus transforming protein E6 (column 2, lines 13-17). Androphy et al. teach the immortalization of cells by the papillomavirus E6 protein and describe the two hybrid assay system to identify human cellular proteins which interact with the viral E6 oncoprotein and could be candidate proteins participating in papillomavirus infectivity and/or transformation (lines 6-16, column 19). Androphy et al. specifically describe the application of a modified yeast two hybrid system in the identification of genes encoding interacting proteins in Example 1 (column 52; limitation of claim 4). Additionally described by Androphy et al. is the use of *in vitro* binding assays using E6 and GST-E6-BP (column 53, the limitation of claim 5). Using these techniques Androphy et al. have identified, isolated and sequenced a series of cellular E6 binding proteins that did not encode either p53 or pRb (Table 1, column 54; the limitations of claims 3 and 6). As the method of Androphy et al. involved sequence analysis, the presence or absence of alterations in the genetic material of the cell could therefore be ascertained (the limitation of claim 13). As the papillomaviruses are a heterogeneous group of DNA tumor viruses, they may be utilized to identify cellular proteins involved in proliferative disease, as “the inactivation of the normal functions of the tumor suppressor proteins pRB and p53 are important steps in human cervical

carcinogenesis, either by mutation or through complex formation with HPV E6 and E7 oncoproteins." (columns 1 and 2, and the limitation of claim 14).

Given the teachings of Freund et al. as stated *supra*, regarding the identification of new tumor suppressor genes, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the differential growth screening method of Freund et al. and the viral protein and cell protein interaction screening method of Androphy et al. to identify a cellular protein involved in the susceptibility to proliferative disease.

Therefore, a person of ordinary skill in the art, would have been motivated to combine the differential growth screening method of Freund et al. and the viral protein and cell protein interaction screening method of Androphy et al., due to the specific teachings of Freund et al., (as outlined *supra*), to identify a cell protein involved in susceptibility to proliferative disease, or to identify the absence or presence of a genetic alteration in said protein, and would have a reasonable expectation of success in the method of identifying a cellular protein involved in the susceptibility to proliferative disease, that is not the Rb or p53 proteins.

Hence, the claimed invention a whole is *prima facie* obvious, absent evidence to the contrary.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending

Application No. 10/828,815. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. The claims of the '815 application are directed to a method of producing tumor host range mutant virus and identifying a mammal at increased risk of acquiring a proliferative disease having a mutation in a protein associated with proliferative disease, that encompass the method of claims 1-9 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

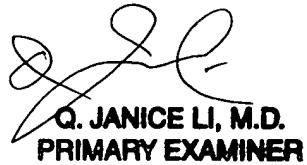
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